Title

Female smokers are at greater risk of airflow obstruction than male smokers: UK Biobank

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At a Glance Commentary

Scientific Knowledge on the Subject: In developed countries, sex differences in prevalence of COPD are becoming less marked and it has been suggested that this may be explained by a steep increase in prevalence of smoking among women. It has also been suggested that among smokers, women are more likely to develop COPD than men. Previous population-based studies have attempted to explore this question, but due to limited data on smoking characteristics (i.e. duration, cigarettes per day, pack-years, age started, time since quitting) evidence for higher smoking-related risk of disease in women remains weak.

What This Study Adds to the Field: This study is the most comprehensive analysis of sex differences in the association of airflow obstruction (hallmark of COPD) with cigarette smoking history. Using data from 149,075 women and 100,252 men who took part in the UK Biobank, we show that women who ever smoked are at a greater risk of airflow obstruction than men who ever smoked in a similar fashion in terms of duration, cigarettes per day, and pack-years. This sex difference was less evident for age of starting and time since quitting. This study also adds to the field by showing that the dose-effect relationship of airflow obstruction with smoking is non-linear both in women and men.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: The prevalence of chronic obstructive pulmonary disease (COPD) is increasing faster among women than among men.

Objectives: To examine sex differences in the risk of airflow obstruction (COPD hallmark) in relation to smoking history.

Methods: We analysed 149,075 women and 100,252 men taking part in the UK Biobank, who had provided spirometry measurements and information on smoking. The association of airflow obstruction with smoking characteristics was assessed, by sex, using regression analysis. The shape of this relationship was examined using restricted cubic splines.

Measurements and main results: The association of airflow obstruction with smoking status was stronger in women (OR_{ex}=1.44; $OR_{current}$=3.45) than in men (OR_{ex}=1.25; $OR_{current}$=3.06) (*P*-interaction=$5.6x10^{-4}$). In both sexes, the association of airflow obstruction with cigarettes/day, duration and pack-years did not follow a linear pattern, with the increase in risk at lower doses being steeper among women. For equal doses of exposure, sex differences were present in both ex- and current smokers for cigarettes/day (*P*-interaction$_{ex}$=$6.0x10^{-8}$; *P*-interaction$_{current}$=$1.1x10^{-5}$), duration (*P*-interaction$_{ex}$=$7.9x10^{-4}$; *P*-interaction$_{current}$=0.004) and pack-years (*P*-interaction$_{ex}$=$6.6x10^{-18}$; *P*-interaction$_{current}$=$1.3x10^{-6}$). Overall those who started smoking before 18 were more likely to have airflow obstruction, but a sex difference in this association was not clear. For equal time since quitting, the reduction in risk among women seemed less marked than among men.

Conclusion: Exposed to the same dose of smoking, women show higher risk of airflow obstruction than men. This could partly explain the increasingly smaller sex difference in the prevalence of COPD, especially in countries where smoking patterns have become similar between women and men.

Abstract word count: 250 **Key words:** airflow obstruction; sex differences; smoking

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third most common cause of death globally and both its prevalence and mortality have been lower in women than in men (1-3). This disparity between sexes has been attributed to differences in environmental and lifestyle exposures, particularly cigarette smoking, which is a major risk factor for COPD (2). These sex differences have more recently become less marked, especially in developed regions where smoking patterns are similar between men and women (3, 4). In the UK, patterns of smoking in women have moved closer to those of men in terms of age of smoking initiation, duration and intensity (5).

It has been suggested that female smokers are more likely to develop COPD than male smokers (6, 7), and that for the same level of exposure to cigarette smoke women have a higher risk of developing more severe disease at younger ages than men (3, 8). Could this be the result of sex-related differences in susceptibility to the harmful effects of tobacco? Several studies have tried to answer this question. A meta-analysis of 11 cohort studies reported a faster decline in the forced expiratory volume in one second (FEV1)% predicted among female smokers than among male smokers (9). Three more recent cross-sectional studies showed that female smokers have a lower FEV1% predicted (8) and a greater risk of an FEV1 to forced vital capacity (FVC) ratio < 70% than male smokers (3, 10). Conversely, a meta-analysis of eight cross-sectional studies showed no sex difference in the effect of cigarette smoking on the FEV1 (11), and a cohort study reported a faster decline in FEV1% predicted among male smokers (12). Furthermore, observed sex differences in the effect of smoking may depend on the definition of airflow obstruction (13). Most studies, to date, assessed the association of “airflow obstruction” using FEV1 as the outcome and a simple categorisation of smoking status (non-, ex-, current smoker) as the exposure of interest. Few have used: 1) the FEV1/FVC ratio to define airflow obstruction; and 2) age of initiation,

duration, cigarettes per day, pack-years and time since quitting to characterise the exposure to cigarette smoking. Overall evidence for higher smoking-related risk of disease in women remains weak.

The aim of this study was to examine the risk of airflow obstruction, a hallmark of COPD, in relation to a self-reported cigarette smoking history (age started smoking, number of cigarettes per day, duration of smoking, pack-years, time since quitting) among women and men in the UK Biobank.

METHODS

Study participants

The UK Biobank is a very large population-based study of adults, aged 40-69 years, recruited from 22 centres across England, Wales and Scotland. Recruitment relied on invitations sent by mail to both women and men, in approximately equal numbers, living within 10 miles (16.1 km) of the testing centre. Between 2006 and 2010, 502,628 participants completed a touchscreen questionnaire to provide information on their lifestyle, medical and family history, and underwent clinical assessment, including spirometry (14-16).

The study was approved by the UK National Research Ethics Service Committee North West – Haydock, and electronic written consent from each participant was obtained.

Airflow obstruction

In each centre, lung function was assessed by nurses or healthcare technicians trained in spirometry following a standard protocol and using a Vitalograph Pneumotrac 6800 spirometer (Vitalograph Ltd., Buckingham, UK). Participants did not perform spirometry if they had, or were unsure whether they had, a lower respiratory tract infection in the last month (i.e., influenza, bronchitis, severe cold, pneumonia), a history of detached retina, a

heart attack or surgery to eyes, chest or abdomen in last three months, a history of collapsed lung, were pregnant (first or third trimester) and/or were currently on medication for tuberculosis. The goal was to record two acceptable blows from a maximum of three attempts. Data analysed in this report are from participants who had provided at least two spirograms fulfilling the following criteria: 1) without cough; 2) back-extrapolated volume <5% FVC (or <150mL if greater); 3) flow <25mL in final 1s of forced expiratory time (FET); 4) both forced expiratory volume in 1s (FEV1) and forced vital capacity (FVC) reproducible; and 5) FET ≥6s on best curve (highest FEV1 + FVC) (figure 1).

The outcome measure, i.e. airflow obstruction, was defined as an FEV1/FVC < lower limit of normal (LLN) for age and height (17), based on reference equations for Caucasians derived from the third US National Health and Nutrition Examination Survey (NHANES).

Smoking history

Information on current and past smoking characteristics, including age started smoking, duration of smoking, number of cigarettes per day, age when stopped smoking (ex-smokers only), was assessed using the touchscreen questionnaire.

The smoking status of participants was defined as: a) current smokers, if they smoked on most or all days; b) ex-smokers, if they had smoked in the past, but have quit; or c) lifetime non-smokers, if they have never smoked or smoked less than 100 cigarettes during their lifetime. Duration of smoking was calculated from the age the participant started smoking and the date of assessment (or, among ex-smokers, the age when the participant stopped smoking). The number of pack-years for ex- and current smokers was calculated by multiplying the number of cigarettes smoked per day by the duration of smoking (years), divided by 20. Time since quitting smoking was determined from the age when the participant stopped smoking and the date of assessment.

Statistical analysis

Following exclusions of participants who had used an inhaler in the last hour prior to spirometry, those whose smoking status was unknown, those who smoked cigars or pipes, and all pregnant women, the final sample for analysis comprised of 149,075 women and 100,252 men.

The association of airflow obstruction with each of the smoking history characteristics (smoking status; cigarettes per day; duration; pack-years; age started smoking; time since quitting smoking) was examined using logistic regression models adjusted for potential confounders: centre, age (continuous), ethnicity (Caucasian, non-Caucasian), standing height (continuous), Townsend deprivation index (continuous), and fresh fruit intake (0-1, 2-3, and 4+ pieces of fruit). To examine the effect of 'age started smoking' we further adjusted the models for the number of cigarettes per day, and among ex-smokers, time since quitting. To assess the effect of 'time since quitting' we further adjusted the initial models for pack-years and age started smoking.

To explore the relationship of airflow obstruction with cigarettes per day, duration of smoking, pack-years, age started smoking (compared to start at 18 years of age, which is the legal age to buy tobacco in the UK), and time since quitting, we used restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the smoking characteristic distribution.

The above analyses were carried out for women and men separately. To test for interactions between sex and each of the smoking characteristics, we ran models including both sexes and an interaction term. These models were adjusted for the same confounders as above. Log-likelihood ratio tests comparing the models with and without the interaction terms were performed to assess whether the interactions were statistically significant.

In a set of sensitivity analyses, we further examined the sex difference in the effect of increasing number of pack-years among current smokers by: 1) adjusting for the top 14 jobs identified as those with moderate/high airflow obstruction increased risk (18); 2) excluding participants with self-reported doctor-diagnosed asthma; 3) excluding non-Caucasians; and 4) excluding Caucasians. In addition, we assessed whether the decline in the FEV1/FVC ratio (continuous) and FEV1 (continuous), as proxies for severity, associated with pack-years was different between women and men among current smokers with airflow obstruction.
Results were accepted as statistically significant when *P* was less than 0.05. Statistical analysis was performed using Stata v.14 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of the 249,327 participants included in this study are presented in table 1. The proportion of ever smokers among women and men were 41% and 52%, respectively. Current smokers were more socioeconomically deprived and ate less fresh fruit than lifetime non-smokers and ex-smokers. The prevalence of airflow obstruction was higher in current smokers (women: 20.6%; men: 19.0%) than in ex-smokers (women: 9.3%; men: 8.8%) and lifetime non-smokers (women: 6.4%; men: 6.7%).
Participants excluded from the analysis due to low quality of spirometric data were similar to those included (supplementary table 1).

Association of airflow obstruction with smoking status

Among women, ex- [odds ratio (OR) = 1.44; 95% confidence interval (CI) 1.38-1.50] and current (OR = 3.45; 95% CI 3.27-3.63) smokers had an increased risk of airflow obstruction compared to lifetime non-smokers (table 2). Among men, the risk of airflow obstruction was also higher in ex- (OR 1.25; 95% CI 1.19-1.32) and current (OR = 3.06; 95% CI 2.87-3.25)

smokers compared to lifetime non-smokers. Overall, the association of airflow obstruction with smoking status was stronger in women than in men (*P* for interaction = $5.6x10^{-4}$).

Association of airflow obstruction with cigarettes per day, duration, and pack-years

The dose-effect relationship of airflow obstruction with cigarettes per day, duration and pack-years was non-linear (figures 2 and 3).

Among ex-smokers, women were at increased risk of airflow obstruction just after 1 cigarette per day and 15 years of smoking, compared to 1 cigarette per day and 20 years of smoking among men. For equal number of cigarettes per day (*P* for interaction = $6.0x10^{-8}$) and years of smoking (*P* for interaction = $7.9x10^{-4}$), women showed greater risk of airflow obstruction than men. The differences between women and men in relation to pack-years combined these two effects, with women becoming at risk of airflow obstruction at lower doses of smoking compared to men (10 vs 19 pack-years). The risk of airflow obstruction, for the same dose of smoking, was greater among women than among men (*P* for interaction = $6.6x10^{-18}$) (figure 2; supplementary table 2).

Among current smokers, the pattern was similar with women showing, for equal number of cigarettes per day (*P* for interaction = $1.1x10^{-5}$), years of smoking (*P* for interaction = 0.004) and pack-years (*P* for interaction = $1.3x10^{-6}$), a higher risk of airflow obstruction than men (figure 3; supplementary table 3). For example, for 10 cigarettes per day, 10 years of smoking and 10 pack-years the risk of airflow obstruction among women was 3.82 (95% CI 3.50-4.16), 1.37 (95% CI 1.29-1.44) and 2.38 (95% CI 2.18-2.61) versus 2.84 (95% CI 2.53-3.19), 1.30 (95% CI 1.22-1.39) and 1.94 (95% CI 1.72-2.19) among men. The increase in the risk of airflow obstruction at low doses of smoking was steeper among women than among men.

Association of airflow obstruction with age started smoking

Among ex- and current smokers, the risk of airflow obstruction was higher in those who started smoking before 18 years of age (except in female ex-smokers who started before the age of 10). The likelihood of having airflow obstruction was significantly higher in female current smokers who started smoking between the ages of 12 and 17. A sex difference in the association of airflow obstruction with age started smoking was not clear (ex-smokers: *P* for interaction = 0.53; current smokers: *P* for interaction = 0.63) (figure 4; supplementary table 4).

Association of airflow obstruction with time since quitting

The risk of airflow obstruction among ex-smokers, as compared to current smokers, was significantly smaller the greater the time since quitting (figure 5; supplementary table 5). After 30 years since quitting, the reduction in risk of airflow obstruction seemed to stagnate. For the same number of years since quitting, the reduction in risk appeared less marked among women than among men, but this difference was not statistically significant (*P* for interaction = 0.098).

Sensitivity analysis

Results were robust after controlling formally for jobs in occupations with moderate/high airflow obstruction risk (supplementary figure 1) and after exclusion of participants with self-reported asthma (supplementary figure 2) and non-Caucasians (supplementary figure 3). Among non-Caucasians, exposure to smoking was generally lower, but the sex difference in the risk of airflow obstruction was broadly similar to that seen in Caucasians (supplementary figure 4).

Among current smokers who have airflow obstruction, the decline in the FEV1/FVC and FEV1 seemed greater for women at lower doses of smoking and for men at higher doses of smoking. However, the interaction between sex and pack-years was not statistically significant (supplementary figures 5 and 6).

DISCUSSION

In this population-based study of adults, the prevalence of airflow obstruction was broadly similar in women and men who did not smoke. However, women who smoked were at a greater risk of airflow obstruction than men who smoked in a similar fashion in terms of cigarettes per day, duration, and pack-years. This sex difference was less evident for age of starting and time since quitting.

This study has several strengths: 1) a very large sample size and the inclusion of 22 centres across the UK; 2) the use of a standardised protocol for spirometry and questionnaire for collection of data across sites; 3) the use of spirometric measurements with the best quality only; and 4) the wealth of data on several smoking characteristics.

This study also has limitations. It is based on self-reported smoking status and characteristics, and there may be sex differences in the reporting of smoking history. If women under-reported smoking, this would lead to overestimation of the true effects among this group. However, it has been shown in population-based studies that self-reported smoking history characteristics are usually accurate among both sexes (19, 20) and that women are more likely than men to provide reliable answers with respect to smoking (21). We could not adjust pack-years for periods of temporary smoking abstinence. However, periods of light or no smoking are particularly true of female smokers, who during pregnancy and when their

children are young are more likely to abstain from smoking. A correction for these periods of smoking abstinence would likely strengthen our findings, making the sex difference in the association of airflow obstruction with smoking history more pronounced. There may be sex differences in inhalation pattern, but this has not been assessed. Heavy smoking, which is associated with increased mortality (22), is more prevalent among men, and in this cross-sectional study it is possible that survival bias has led to a dilution of the association of airflow obstruction with cigarette smoking mainly among men. However, the proportion of men who smoked 21 cigarettes, or more, per day was considerably higher than among women (ex-smokers: 28.0% men vs 13.3% women; current smokers: 18.3% men vs 8.6% women) suggesting survival bias was not a major concern. At testing centres, the American Thoracic Society/European Respiratory Society recommendation of performing at least three manoeuvres to measure FVC and FEV1 was not strictly followed, but we used only spirometric data that satisfied all other within- and between-manoeuvre criteria (23). Exclusion from spirometric assessment of participants reporting a transient lower respiratory tract infection is commonly adopted in epidemiological studies. Since people with obstructive lung conditions may have more frequent respiratory infections, they may be more likely than those without to be excluded from lung function testing. In this study, we could not assess whether this was true or not as information on the precise contra-indication for spirometry was not collected. Although not impossible, it seems unlikely that this would lead to the sex differences that we report here. We are aware that the UK Biobank may not be representative of the general population (24). However, our findings are not descriptive, rather they regard to risk of airflow obstruction associated with smoking history and are internally valid, which is of greater relevance than representativeness when inferring causality (25, 26).

To date, this very large study is the most comprehensive analysis of sex differences in the association of airflow obstruction with cigarette smoking history. Our findings are consistent with most previous reports from other population-bases studies, although the outcome definition varied across studies. In the Copenhagen City Heart Study and Glostrup Population Studies (6) and Bronchial Obstruction in Nord-Trondelag study (27), for the same number of pack-years, female smokers had lower FEV1 than male smokers. In contrast, in the Harvard Six Cities study, for an equal smoking dose, male smokers showed a greater decline in FEV1 than female smokers (28). In the Burden of Lung Disease study (3) and in the Danish studies (6), female smokers had a higher risk of COPD and hospitalisation for COPD than male smokers with same number of pack-years. In the Kadoorie Biobank study (10), for a similar number of cigarettes per day and age of starting smoking, female smokers had a higher risk of airflow obstruction than male smokers. Among people who started smoking before the age of 18 years and especially after 12 years of age, female current smokers seem to be at a greater risk of airflow obstruction than male current smokers. Although the sex difference in the association of airflow obstruction with age started smoking among current smokers was not statistically significant, it is in line with a report from the Harvard Six Cities study in adolescents where, among smokers, girls showed a slower lung function growth than boys (29).

A non-linear decline in FEV1 in relation to increasing pack-years has been reported previously, but sex differences were not examined (30). We add to the literature by showing that the dose-effect relationship of airflow obstruction (FEV1/FVC<LLN) with smoking is non-linear both in women and men. Our findings show that the major and faster increase in the risk of airflow obstruction occurs at lower doses of smoking, and that smoking ≥21 cigarettes per day and having smoked for ≥15-20 pack-years (≥30-35 pack-years among ex-

smokers) is of less additional impact on the likelihood of having airflow obstruction. This suggests that heavy smokers may inhale less than light smokers (31) or they may have a genetic variant that provides them some level of protection from airflow obstruction (32).

The biological mechanisms underlying the apparent greater susceptibility to cigarette smoke among women are unclear. It may be that: 1) the concentration of cigarette smoke per unit of area of airway, for the same level of exposure and same lung volume, is greater in women than in men, as women have a smaller airway to lung volume ratio than men (33); 2) there is a genetic predisposition for increased smoke-related lung damage among women that is linked to the X chromosome (34); and/or 3) there are hormonally-mediated differences in the metabolism of cigarette smoke (35, 36). In a mouse model of COPD exposed to chronic cigarette smoke, female animals showed greater small airway wall remodelling, with increased oxidative stress and TGF-beta 1 signalling, than male mice and females ovariectomized before smoke exposure (37). This observation suggests that sex hormones are responsible for the differences in smoking-related risk of airflow obstruction between male and female smokers.

In summary, among ever smokers the prevalence of airflow obstruction is higher in women than men, and for the same dose of smoking exposure, women are at greater risk of airflow obstruction than men. With increasing rates of smoking among women in both developed and developing countries, it is important to create anti-tobacco campaigns specifically targeting this group since they are more susceptible to the effects of cigarette smoking.

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CONFLICT OF INTEREST

None to declare.

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The funder of this study had no role in study design, data analysis and interpretation of results, or writing of the manuscript.

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Tables' titles

Table 1. Characteristics of participants in UK Biobank included in this study.

Table 2. Association of airflow obstruction with smoking status.

Supplementary table 1. Characteristics of participants in UK Biobank excluded from this study.

Supplementary table 2. Association of airflow obstruction with duration and intensity of smoking in ex-smokers compared with lifetime non-smokers.

Supplementary table 3. Association of airflow obstruction with duration and intensity of smoking in current smokers compared with lifetime non-smokers.

Supplementary table 4. Association of airflow obstruction with age at which participants started smoking.

Supplementary table 5. Association of airflow obstruction with time since quitting smoking.

Figures' titles

Figure 1. Selection of participants in the study.

Figure 2. Association of airflow obstruction with cigarettes per day (p-interaction = $6.0x10^{-8}$; upper row), smoking duration (p-interaction = $7.9x10^{-4}$; middle row), and pack-years (p-interaction = $6.6x10^{-18}$; lower row) among ex-smokers. Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, and fresh fruit intake. Reference group: Lifetime non-smokers. Shaded area represents 95% confidence interval. Bars show the distribution of smoking characteristic (i.e cigarettes per day, smoking duration, and pack-years) among ex-smokers.

Figure 3. Association of airflow obstruction with cigarettes per day (p-interaction = $1.1x10^{-5}$; upper row), smoking duration (p-interaction = 0.004; middle row), and pack-years (p-interaction = $1.3x10^{-6}$; lower row) among current smokers. Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, and fresh fruit intake. Reference group: Lifetime non-smokers. Shaded area represents 95% confidence interval Bars show the distribution of smoking characteristic (i.e cigarettes per day, smoking duration, and pack-years) among current smokers.

Figure 4. Association of airflow obstruction with age at smoking initiation among ex-smokers (p-interaction = 0.53; upper row) and among current smokers (p-interaction = 0.63; lower row). Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, fresh fruit intake, and cigarettes per day (and, among ex-smokers, time since quitting). Reference group: Participants who started smoking at age 18 years. Shaded area represents 95% confidence interval. Bars show the distribution of age started smoking among study participants.

Figure 5. Association of airflow obstruction with time since quitting smoking (p-interaction = 0.098). Adjusted for centre, age, ethnicity, standing height, Townsend

deprivation index, fresh fruit intake, pack-years, and age started smoking. Reference group: Current smokers. Shaded area represents 95% confidence interval. Bars show the distribution of time since quitting among ex-smokers.

Table 1. Characteristics of participants in UK Biobank included in this study.

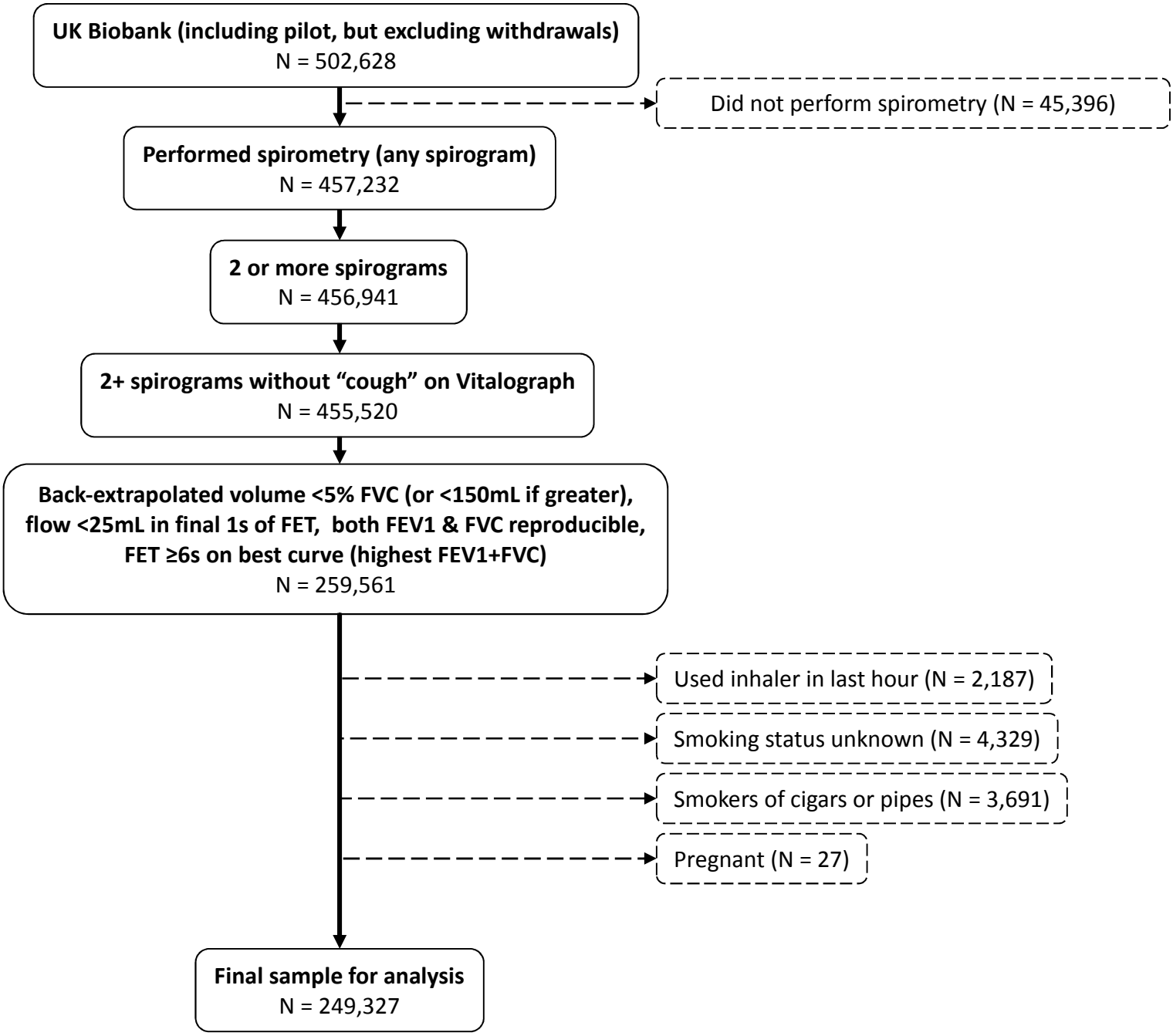
	Women (N = 149,075)			**Men (N = 100,252)**			**Total population**
	Lifetime non-smokers	**Ex-smoker**	**Current smoker**	**Lifetime non-smokers**	**Ex-smoker**	**Current smoker**	
N	88,612	47,176	13,287	48,576	40,205	11,471	249,327
Age (years), median (IQR)	57 (50-62)	59 (52-63)	54 (48-61)	56 (48-62)	60 (53-65)	54 (47-61)	57 (50-63)
Height (cm), median (IQR)*	162 (158-166)	163 (158-167)	162 (158-167)	176 (171-180)	175 (171-180)	175 (170-179)	167 (161-174)
Ethnicity (%)							
Caucasian	94.1	97.6	95.2	93.9	96.4	92.4	95.1
Non-Caucasian	5.9	2.4	4.8	6.1	3.6	7.6	4.9
Age started smoking (years), median (IQR)**	-	17 (16-19)	17 (15-19)	-	16 (15-18)	16 (15-18)	17 (15-18)
Duration smoked (years), median (IQR)***	-	20 (12-30)	36 (29-43)	-	21 (13-30)	36 (29-44)	25 (15-35)
Cigarettes smoked daily, median (IQR)‡	-	15 (10-20)	15 (10-20)	-	20 (15-25)	15 (10-20)	20 (10-20)
Pack-years, median (IQR)†	-	15.0 (7.5-25.5)	23.0 (13.6-34.0)	-	19.0 (10.0-33.0)	27.6 (16.4-41.0)	18.8 (10.0-31.2)
Body mass index (kg/m^2), median (IQR) ¥	25.9 (23.3-29.4)	26.4 (23.8-29.9)	25.8 (23.2-29.2)	26.8 (24.7-29.5)	27.8 (25.5-30.5)	26.8 (24.3-29.5)	26.6 (24.0-29.7)
Townsend deprivation index, median (IQR)€	-2.5 (-3.8, -0.2)	-2.0 (-3.6, 0.6)	-0.5 (-2.8, 2.6)	-2.5 (-3.8, -0.2)	-2.2 (-3.7, 0.3)	-0.5 (-2.9, 2.7)	-2.2 (-3.7, 0.3)
Fresh fruit daily intake, %							
0-1 pieces	27.3	28.7	48.9	40.7	41.4	60.6	35.1
2-3 pieces	54.4	52.1	40.3	45.3	44.1	31.3	48.7
4+ pieces	18.3	19.2	10.8	14.0	14.5	8.1	16.2
FVC (L), median (IQR)	3.15 (2.76-3.56)	3.14 (2.75-3.55)	3.09 (2.66-3.52)	4.47 (3.92-5.03)	4.29 (3.75-4.85)	4.30 (3.72-4.89)	3.53 (2.97-4.26)
FEV1 (L), median (IQR)	2.43 (2.11-2.76)	2.39 (2.07-2.73)	2.30 (1.93-2.67)	3.42 (2.97-3.87)	3.23 (2.78-3.69)	3.16 (2.65-3.67)	2.69 (2.25-3.24)
FEV1/FVC < LLN (%)	6.4	9.3	20.6	6.7	8.8	19.0	8.7

IQR, interquartile range. *225 missing. **34,883 missing. ***32,729 missing. ‡32,621 missing. †33,326 missing. ¥3,364 missing. €313 missing.

Table 2. Association of airflow obstruction with smoking status.

	Women			Men			
	N	**% airflow obstruction**	**OR (95% CI)**	**N**	**% airflow obstruction**	**OR (95% CI)**	***P-interaction***
Smoking status							
Lifetime non-smokers	88,459	6.4	Ref.	48,416	6.7	Ref.	$5.6x10^{-4}$
Ex-smokers	47,101	9.3	1.44 (1.38-1.50)	40,124	8.8	1.25 (1.19-1.32)	
Current smokers	13,250	20.6	3.45 (3.27-3.63)	11,440	19.0	3.06 (2.87-3.25)	

Model 1: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, and fresh fruit intake.



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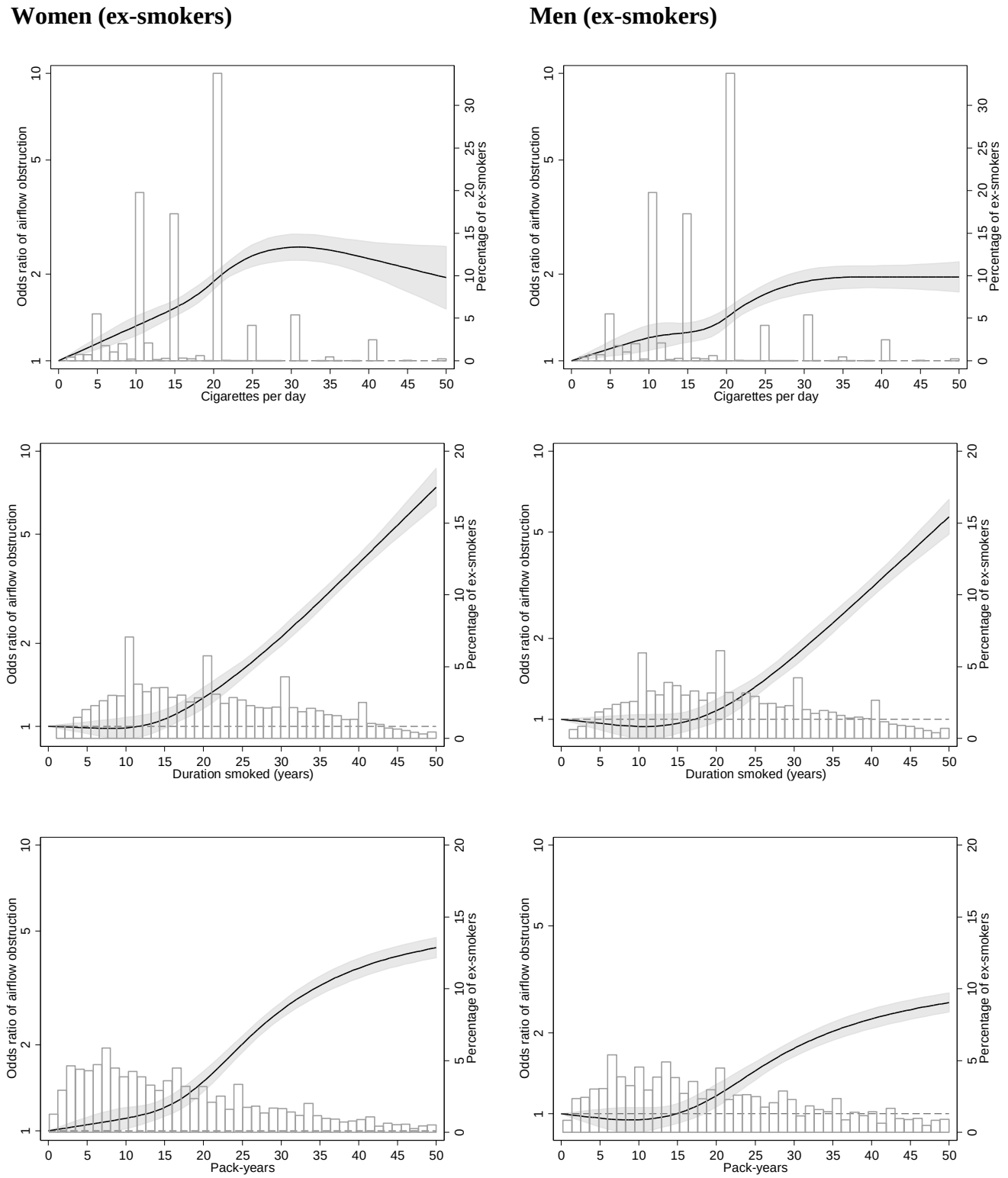

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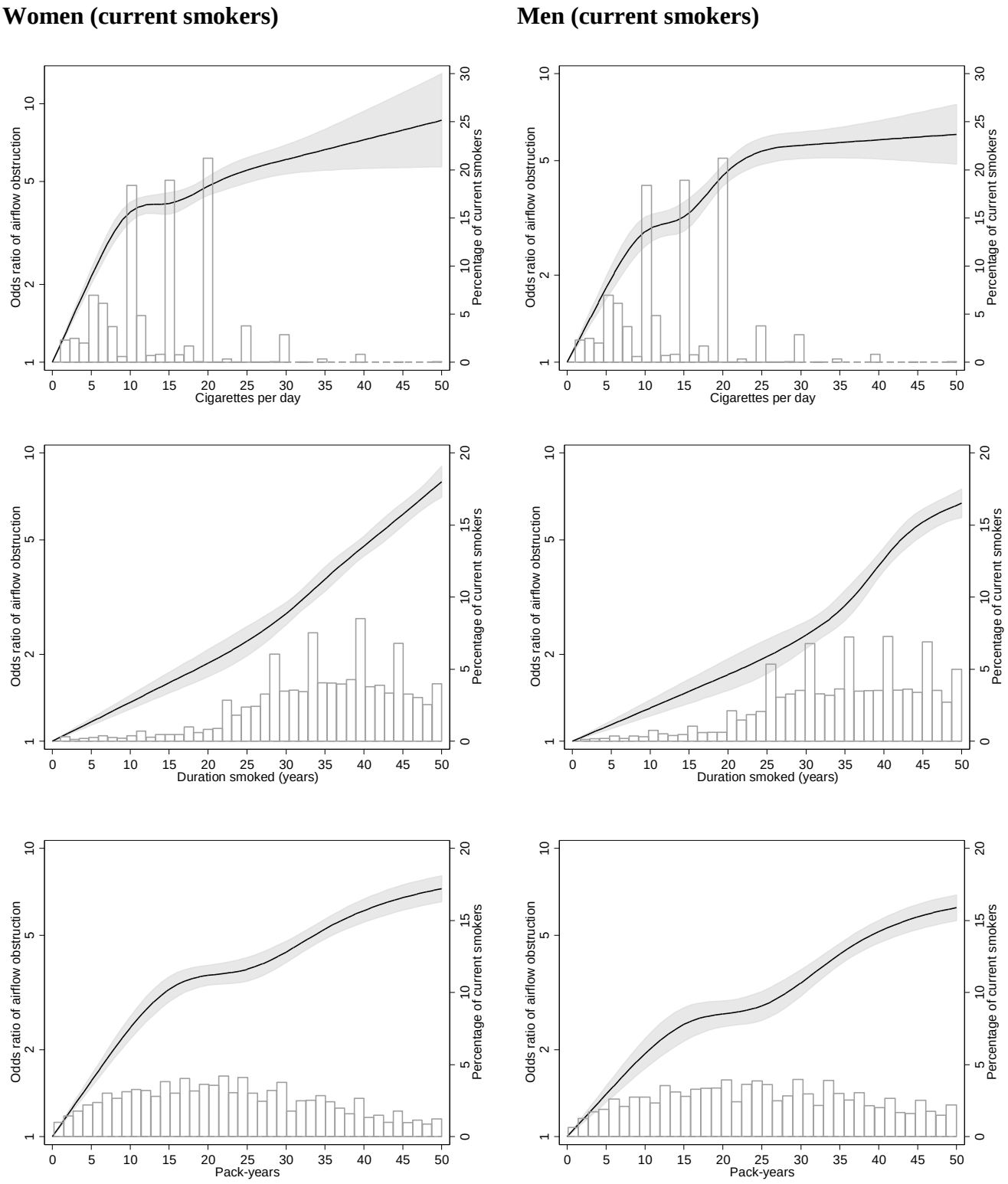

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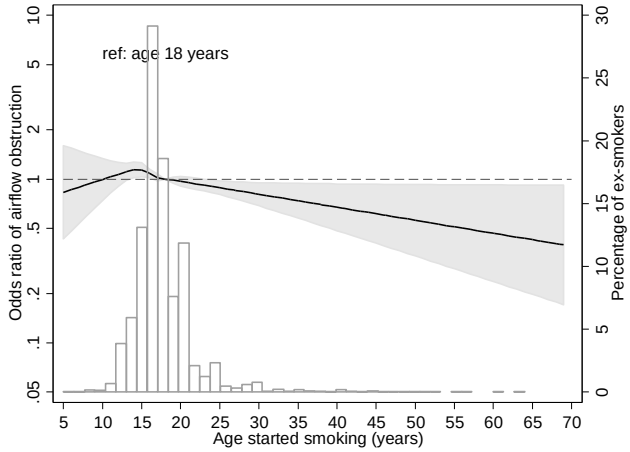
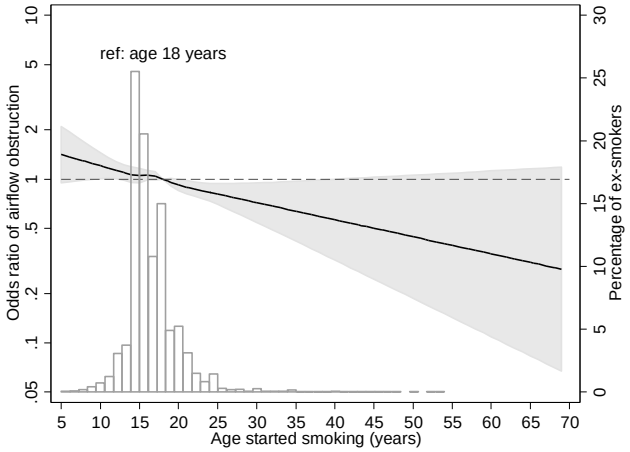
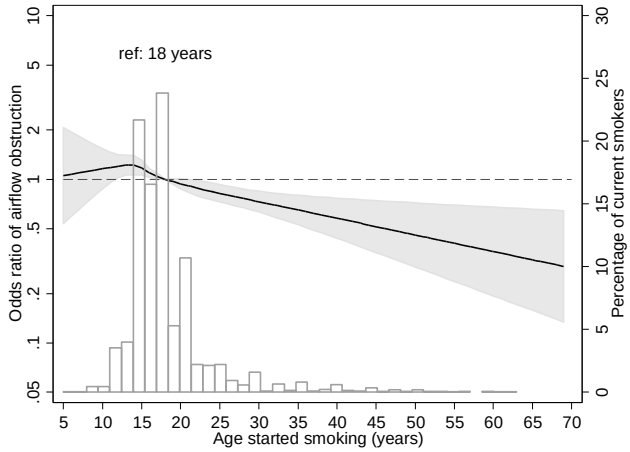
Women (ex-smokers)



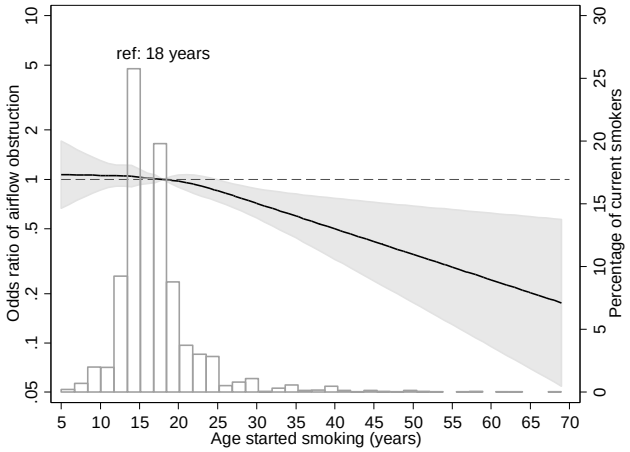
Men (ex-smokers)



Women (current smokers)



Men (current smokers)



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Women (vs current smokers) **Men (vs current smokers)**

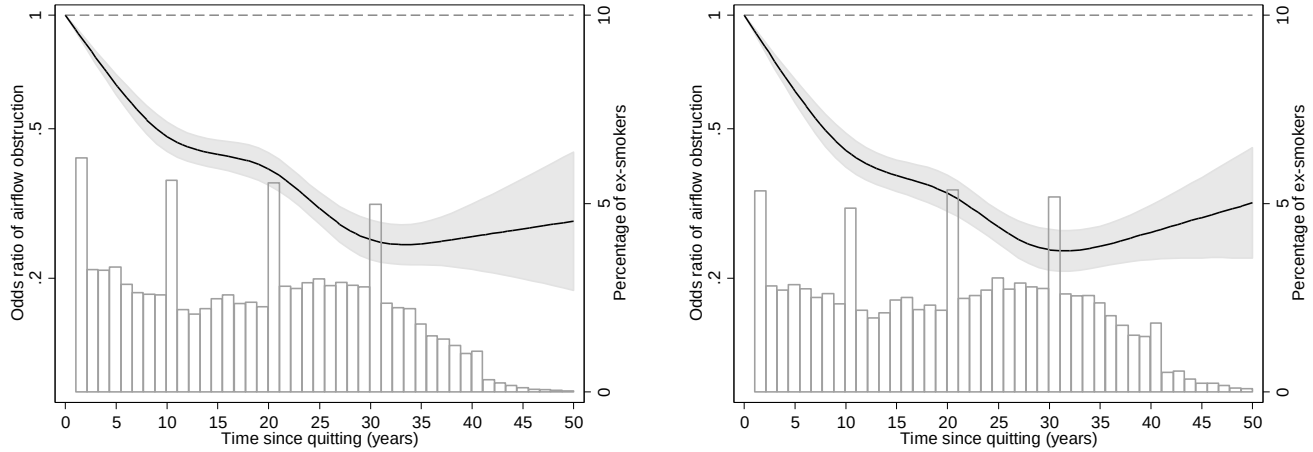

Figure 5. Association of airflow obstruction with time since quitting smoking (p-interaction = 0.098). Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, fresh fruit intake, pack-years, and age started smoking. Reference group: Current smokers. Shaded area represents 95% confidence interval. Bars show the distribution of time since quitting among ex-smokers.